09/919,195

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FILE 'HOME' ENTERED AT 09:13:52 ON 18 MAR 2003

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(FILE 'HOME' ENTERED AT 09:13:52 ON 18 MAR 2003)

FILE 'CA' ENTERED AT 09:13:58 ON 18 MAR 2003
L1 136887 S LUNG
L2 2349 S ALVEOLI
L3 1993 S ATRA
L4 4106 S ALL-TRANS-RETINOIC ACID
L5 4119 S ALL-TRANS-RETINOIC
L6 3335 S RAR
L7 243391 S MODULAT?
L8 431 S L6 AND L7
L9 295 S L8 AND PY<2000

=> s l9 and (l1 or l2 or l3 or l5)
L10 103 L9 AND (L1 OR L2 OR L3 OR L5)

=> d 103 ibib abs kwic

L10 ANSWER 103 OF 103 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 112:230122 CA
TITLE: Indirect effects of histamine on pulmonary rapidly adapting receptors in cats
AUTHOR(S): Yu, Jun; Roberts, Andrew M.
CORPORATE SOURCE: Sch. Med., Univ. Louisville, Louisville, KY, 40292, USA
SOURCE: Respiration Physiology (**1990**), 79(2), 101-10
CODEN: RSPYAK; ISSN: 0034-5687
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The relative importance of **lung** mech. changes during histamine-induced activation of pulmonary rapidly adapting receptors (RARs) was investigated. In anesthetized, open-chest, artificially ventilated cats, the authors recorded **RAR** activity and injected histamine (25-50 .mu.g/kg) into the right atrium. Histamine initially increased **RAR** activity from 1.1 to 3.6 imp/s at 15.6 s when dynamic **lung** compliance (CDYN) was decreased by 29.1%. The firing pattern of RARs changed from a relatively irregular pattern to a pronounced respiratory **modulation**. **RAR** activity reached its peak (5.6 imp/s) at 36.3 s. The firing pattern further changed to a cardiac **modulation**, and the activity closely correlated with cardiac output. On comparing the initial response of RARs to histamine with the response to mech. decreasing CDYN, the activities were similar when CDYN was decreased by the same amt. In cats, the initial increase of **RAR** activity in response to histamine is apparently related to **lung** mech. changes, but the later increase is related to cardiovascular functions.
SO Respiration Physiology (**1990**), 79(2), 101-10
CODEN: RSPYAK; ISSN: 0034-5687
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ST histamine **lung** rapidly adapting receptor; cardiovascular system **lung** histamine; receptor **lung** compliance histamine

IT Blood pressure
(histamine effect on, **lung** rapidly adapting receptors in relation to)

IT **Lung**, composition
(rapidly adapting receptors of, histamine effect on)

IT 51-45-6, Histamine, biological studies
RL: BIOL (Biological study)
(**lung** rapidly adapting receptors response to)

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(FILE 'HOME' ENTERED AT 09:13:52 ON 18 MAR 2003)

FILE 'CA' ENTERED AT 09:13:58 ON 18 MAR 2003
L1 136887 S LUNG
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L8 431 S L6 AND L7
L9 295 S L8 AND PY<2000
L10 103 S L9 AND (L1 OR L2 OR L3 OR L5)

FILE 'STNGUIDE' ENTERED AT 09:16:29 ON 18 MAR 2003

FILE 'CA' ENTERED AT 09:16:43 ON 18 MAR 2003

=> d l10 100-102 kwic

L10 ANSWER 100 OF 103 CA COPYRIGHT 2003 ACS
SO Cell (Cambridge, MA, United States) (**1992**), 68(2), 397-406
CODEN: CELLB5; ISSN: 0092-8674
AB **all-trans Retinoic** acid (RA) has previously been shown to **modulate** the transcriptional properties of the retinoic acid receptor (**RAR**) and retinoid X receptors (RXR). The inability of all-trans RA to bind to RXR suggests that it may be metabolized. . .
IT Receptors
RL: BIOL (Biological study)

(**RAR**-.alpha. (retinoic acid receptor .alpha.), activation of, by cis- and all-trans-retinoates, retinoate distribution in mammal in relation to)

IT Retinoids
RL: BIOL (Biological study)
(**RAR**-.alpha. receptors, activation of, by cis- and all-trans-retinoates, retinoate distribution in mammal in relation to)

IT Isomerization
(cis-trans, photochem., of retinoate, distribution in mammal and activation of retinoate receptors RXR.alpha. and **RAR**.alpha. in relation to)

IT 302-79-4, **all-trans Retinoic** acid
RL: BIOL (Biological study)
(retinoic acid receptors RXR.alpha. and **RAR**.alpha. activation by, cis-retinoate in relation to)

L10 ANSWER 101 OF 103 CA COPYRIGHT 2003 ACS

TI **All-trans retinoic** acid **modulates** the retinoic acid receptor-.alpha. in promyelocytic cells

SO Journal of Clinical Investigation (**1991**), 88(6), 2150-4
CODEN: JCINAO; ISSN: 0021-9738

AB It was recently demonstrated that **all-trans retinoic** acid (RA), the active metabolite of vitamin A, is an efficient alternative to chemotherapy in the treatment of acute promyelocytic leukemia (AML3). It was further shown that, in these AML3 cells, the gene of the retinoic acid receptor-.alpha. (**RAR** .alpha.) is translocated from chromosome 17 to chromosome 15, and fused to a new gene, PLM. This results in the expression of both normal and chimeric **RAR**.alpha. transcripts in AML3 cells. The PLM-**RAR**.alpha. protein may account for the impairment of differentiation and thus leukemogenesis, but not for the paradoxical efficacy of RA in. . . an attempt to elucidate RA's differentiative effect in AML3 patients, the present work examd. the in vitro and in vivo **modulation** of the normal **RAR**.alpha. transcripts by all-trans RA in seven cases of AML3. In all samples, Northern blot anal. revealed a low expression of the two normal **RAR**.alpha. transcripts compared with other human myeloid leukemic cells. No **modulation** was obsd. after 4-8 d of in vivo therapy with all-trans RA 45 mg/m2 per d. In vitro incubation with all-trans RA, however, increased the level of expression of the normal **RAR**.alpha. transcripts in AML3 cells but not in other AML leukemic subtypes. This **modulation** of the two normal **RAR**.alpha. transcripts appeared to be an early and primary event of RA's differentiating effect. Apparently, up-regulation of the normal **RAR**.alpha. gene expression by pharmacol. concns. of all-trans RA may restore the normal differentiation pathway in these cells.

IT Receptors
RL: BIOL (Biological study)
(**RAR**-.alpha. (retinoic acid receptor .alpha.), in promyelocytic leukemia of humans inhibition by retinoic acid)

IT Retinoids
RL: BIOL (Biological study)
(**RAR**-.alpha. receptors, in promyelocytic leukemia of humans inhibition by retinoic acid)

L10 ANSWER 102 OF 103 CA COPYRIGHT 2003 ACS

TI **Modulation** by retinoids of mRNA levels for nuclear retinoic acid receptors in murine melanoma cells

SO Molecular Endocrinology (**1990**), 4(10), 1546-55
CODEN: MOENEN; ISSN: 0888-8809

AB . . . S91-C2 melanoma cells. Specific alterations in gene expression are a plausible mechanism for these effects. Since nuclear retinoic acid receptors (**RAR**) are likely mediators of retinoid-induced changes in gene expression, Northern blotting was used to analyze the expression of **RAR**.alpha., **RAR**.beta., and **RAR**.gamma. in S91-C2 cells. MRNA for both **RAR**.alpha. and **RAR**.gamma. was detected in these cells, but no **RAR**.beta. mRNA could be found. Treatment with 10-7 and 10-6M .beta.-**all-trans** -**retinoic** acid (RA) for 24 h caused a 1.5-2-fold increase in **RAR**.alpha. and **RAR**.gamma. mRNA, whereas lower concns. of RA were ineffective. **RAR**.beta. mRNA, which was undetectable in untreated cells, was detected after 24 h of treatment with a RA concn. as low as 10-9M, and its level increased with up to 10-6M RA. At the latter dose, **RAR**.beta. mRNA induction occurred by 4 h and increased progressively, reaching a plateau after 24 h of treatment. **RAR** .beta. mRNA induction at 4 h was not inhibited by cycloheximide at a concn. that suppressed protein synthesis by more than. . . Several retinoids and related synthetic compds., including 13-cis RA, TTNPB, Ch55, Am80, and the trifluoromethylnonyloxyphenyl analog of RA, also induced **RAR**.beta. mRNA, whereas a 24-h treatment with 10-6M retinol, TTNP (a decarboxylated analog of TTNPB), or the Ph analog of RA failed to induce **RAR**.beta. mRNA. With the exception of retinol and the trifluoromethyl nonyloxyphenyl analog of RA, the ability of the retinoids to induce **RAR**.beta. mRNA and their growth inhibitory effect were correlated. However, S91-C154, a RA-resistant mutant subclone derived from S91-C2 cells, showed mRNA levels of **RAR**.alpha. and **RAR**.gamma. and induction of **RAR**.beta. by RA similar to those detected in the sensitive S91-C2 cells. Like the S91 melanoma cells, two other mouse melanoma cell lines, K-1735P and B16-F1, constitutively expressed **RAR**.alpha. and **RAR**.gamma. mRNAs. The level of **RAR**.beta. mRNA was increased by RA only in B16-F1 cells, although the growth of both was inhibited by RA. These results. . .

ST nucleus retinoate receptor mRNA **modulation** retinoid

IT Animal cell line
(S91-C2 melanoma, mRNA for nuclear retinoic acid receptors of, retinoids **modulation** of)

=> d ibib abs kwic 1-16

L18 ANSWER 1 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 132:88534 CA
TITLE: Electrophysiological and pharmacological analysis of synaptic inputs to pulmonary rapidly adapting receptor relay neurons in the rat
AUTHOR(S): Ezure, Kazuhisa; Tanaka, Ikuko; Miyazaki, Makoto
CORPORATE SOURCE: Department of Neurobiology, Tokyo Metropolitan Institute for Neuroscience, Fuchu, Tokyo, 183-8526, Japan
SOURCE: Experimental Brain Research (**1999**), 128(4), 471-480
CODEN: EXBRAP; ISSN: 0014-4819
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The information from pulmonary rapidly adapting stretch receptors (RARs) to the central nervous system (CNS) is relayed in the nucleus tractus solitarii (NTS). The second-order neurons in the NTS referred to as **RAR** cells have recently been shown to receive rhythmic inputs from

the central respiratory system in addn. to the main inputs from **RAR** afferents. The present study analyzed these synaptic inputs by intracellular recordings from **RAR** cells, and by extracellular recordings combined with local applications of neuroactive drugs to **RAR** cells, in Nembutal-anesthetized, paralyzed, and artificially ventilated rats. The intracellular anal. identified both excitatory postsynaptic potentials (EPSPs) elicited presumably by **RAR** afferents and inhibitory postsynaptic potentials (IPSPs) synchronous with central inspiratory activity. This inhibitory input, called I suppression, was the origin of respiratory **modulation** of **RAR** cell firing, and its time course suggested that some unidentified inspiratory neurons with an augmenting firing pattern were the source of the inhibition. The pharmacol. anal. suggested the types of neurotransmitters used in these synaptic events. First, glutamate was shown to be the primary neurotransmitter at the synapse between **RAR** afferents and **RAR** cells. Iontophoretic applications of the non-NMDA glutamate antagonist, CNQX, abolished **RAR** cell firing almost completely in response to **lung** inflation and deflation and to elec. stimulation of the vagus nerve. Second, glycinergic inputs which inhibited **RAR** cells in the inspiratory phase were revealed by applications of the glycine antagonist, strychnine. I.e., the I suppression was greatly diminished by applications of strychnine. Third, although applications of the GABAA receptor antagonist, bicuculline, had little effect on I suppression, bicuculline markedly increased the baseline firing of **RAR** cells. These results imply that the information path from RARs to the CNS is regulated at the level of **RAR** cells by phasically-acting glycinergic inhibition in the inspiratory phase and tonically-acting GABAergic inhibition; the results also provide new insights into the neuronal mechanisms of **RAR**-induced reflexes.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Experimental Brain Research (**1999**), 128(4), 471-480
CODEN: EXBRAP; ISSN: 0014-4819

AB The information from pulmonary rapidly adapting stretch receptors (RARs) to the central nervous system (CNS) is relayed in the nucleus tractus solitarii (NTS). The second-order neurons in the NTS referred to as **RAR** cells have recently been shown to receive rhythmic inputs from the central respiratory system in addn. to the main inputs from **RAR** afferents. The present study analyzed these synaptic inputs by intracellular recordings from **RAR** cells, and by extracellular recordings combined with local applications of neuroactive drugs to **RAR** cells, in Nembutal-anesthetized, paralyzed, and artificially ventilated rats. The intracellular anal. identified both excitatory postsynaptic potentials (EPSPs) elicited presumably by **RAR** afferents and inhibitory postsynaptic potentials (IPSPs) synchronous with central inspiratory activity. This inhibitory input, called I suppression, was the origin of respiratory **modulation** of **RAR** cell firing, and its time course suggested that some unidentified inspiratory neurons with an augmenting firing pattern were the source of the inhibition. The pharmacol. anal. suggested the types of neurotransmitters used in these synaptic events. First, glutamate was shown to be the primary neurotransmitter at the synapse between **RAR** afferents and **RAR** cells. Iontophoretic applications of the non-NMDA glutamate antagonist, CNQX, abolished **RAR** cell firing almost completely in response to **lung** inflation and deflation and to elec. stimulation of the vagus nerve. Second, glycinergic inputs which inhibited **RAR** cells in the inspiratory phase were revealed by applications of the glycine antagonist, strychnine. I.e., the I suppression was greatly diminished by applications of

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IT **Lung**
Reflex
Synapse
(electrophysiol. and pharmacol. anal. of synaptic inputs to pulmonary rapidly adapting receptor relay neurons in rat)

IT **Breathing** (animal)
(inspiratory phase; electrophysiol. and pharmacol. anal. of synaptic inputs to pulmonary rapidly adapting receptor relay neurons in rat)

L18 ANSWER 2 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 132:88293 CA
TITLE: Retinoic acid: its metabolism and mechanism of action
AUTHOR(S): Kwiatkowska, Danuta; Kwiatkowska-Korczak, Janina
CORPORATE SOURCE: Zaklad Biochem, Akad. Med., Wroclaw, Pol.
SOURCE: Postepy Biologii Komorki (**1999**), 26(3), 579-592
CODEN: PBKODV; ISSN: 0324-833X
PUBLISHER: Fundacja Biologii Komorki i Biologii Molekularnej
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Polish

AB A review with 91 refs. Retinoic acid, a potent morphogen, regulates cell growth and differentiation in embryo and adults. Also, it **modulates** function of many hormones and enzymes. In liver it is derived from carotene, in other tissues - from retinol. Retinoic acid is present as all-trans, 9-cis and 13-cis isoforms. In cytoplasm they are bound by proteins CRABP I and II. Nuclear receptors of retinoic acid, **RAR** and RXR, belong to the superfamily of ligand inducible transcription factors, that include receptors of steroid hormones, thyroxine and vitamin D. Receptors of the **RAR** class interact with all retinoic acid isomers, RXR - with 9-cis-form only. Three isoforms - .alpha., .beta. and .chi. - of both classes are present in cells. Only heterodimer **RAR**/RXR is biol. active. It is bound to the response elements in DNA, consisting of two AGGTCA direct repeats, sepd. by two or five nucleotides. This interaction stimulates transactivity function of the receptor, resulting in induction or repression of target genes. Modifications of the receptor isoform presence and localization, for instance lack of **RAR**.beta., was found in many tumors. Growth inhibition and differentiation induction was obsd. after retinoid treatment in leukemic, breast and **lung** cancer, teratocarcinoma and other malignant tissues.

SO Postepy Biologii Komorki (**1999**), 26(3), 579-592
CODEN: PBKODV; ISSN: 0324-833X

AB A review with 91 refs. Retinoic acid, a potent morphogen, regulates cell growth and differentiation in embryo and adults. Also, it **modulates** function of many hormones and enzymes. In liver it is derived from carotene, in other tissues - from retinol. Retinoic acid is present as all-trans, 9-cis and 13-cis isoforms. In cytoplasm they are bound by proteins CRABP I and II. Nuclear receptors of retinoic acid, **RAR** and RXR, belong to the superfamily of ligand inducible transcription factors, that include receptors of steroid hormones, thyroxine and vitamin D. Receptors of the **RAR** class interact with all retinoic acid isomers, RXR - with 9-cis-form only. Three

isoforms - .alpha., .beta. and .chi. - of both classes are present in cells. Only heterodimer **RAR**/RXR is biol. active. It is bound to the response elements in DNA, consisting of two AGGTCA direct repeats, sepd. by two or five nucleotides. This interaction stimulates transactivity function of the receptor, resulting in induction or repression of target genes. Modifications of the receptor isoform presence and localization, for instance lack of **RAR**.beta., was found in many tumors. Growth inhibition and differentiation induction was obsd. after retinoid treatment in leukemic, breast and **lung** cancer, teratocarcinoma and other malignant tissues.

ST review retinoate metab **RAR** RXR cell proliferation; retinoic acid receptor cell differentiation tumor review

L18 ANSWER 3 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 132:87849 CA

TITLE: Nuclear retinoid acid receptor beta in bronchial epithelium of smokers before and during chemoprevention

AUTHOR(S): Xu, Xiao-Chun; Lee, Jin S.; Lee, J. Jack; Morice, Rodolfo C.; Liu, Xiaoming; Lippman, Scott M.; Hong, Waun K.; Lotan, Reuben

CORPORATE SOURCE: Department of Clinical Cancer Prevention, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA

SOURCE: Journal of the National Cancer Institute (**1999**), 91(15), 1317-1321
CODEN: JNCIEQ; ISSN: 0027-8874

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Retinoids can reverse neoplastic lesions and prevent second primary tumors in the aerodigestive tract. These effects are thought to be mediated by nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs), each receptor group including three subtypes (.alpha., .beta., and .gamma.). Previously, we found that **RAR**.beta. expression was suppressed in **lung** cancer. In this study, we investigated whether expression of **RAR**.beta. is **modulated** by chemopreventive intervention. Methods: Using in situ hybridization, we analyzed **RAR**.beta. mRNA (mRNA) expression in bronchial biopsy specimens from heavy smokers, at baseline and after 6 mo of treatment with 13-cis-retinoic acid (13-cis-RA) or placebo. Since we had previously detected **RAR**.beta. expression in 90% of bronchial specimens from nonsmokers, we considered loss of **RAR**.beta. mRNA expression in at least one of six biopsy specimens at baseline in this study to be aberrant. Results: **RAR**.beta. mRNA expression was aberrant in 30 (85.7%) of 35 subjects in the 13-cis-RA group and in 24 (72.7%) of 33 subjects in the placebo group. After 6 mo of 13-cis-RA treatment, the no. of subjects who were **RAR**.beta. pos. in all six biopsy specimens increased from five of 35 to 13 of 35 (2.6-fold), so that the percentage of individuals with aberrant **RAR**.beta. expression decreased to 62.9% (22 of 35), which represents a statistically significant difference from baseline expression (two-sided P = .01). In the placebo group, no statistically significant difference in **RAR**.beta. expression was obsd. between baseline and 6 mo. **RAR**.beta. expression was not related to current smoking status or reversal of squamous metaplasia. Conclusions: These results indicate that **RAR**.beta. is an independent marker of response to 13-cis-RA and may serve as an intermediate biomarker in chemoprevention trials of upper aerodigestive tract cancers.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Journal of the National Cancer Institute (**1999**), 91(15), 1317-1321
CODEN: JNCIEQ; ISSN: 0027-8874

AB Background: Retinoids can reverse neoplastic lesions and prevent second primary tumors in the aerodigestive tract. These effects are thought to be mediated by nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs), each receptor group including three subtypes (.alpha., .beta., and .gamma.). Previously, we found that **RAR**.beta. expression was suppressed in **lung** cancer. In this study, we investigated whether expression of **RAR**.beta. is **modulated** by chemopreventive intervention. Methods: Using in situ hybridization, we analyzed **RAR**.beta. mRNA (mRNA) expression in bronchial biopsy specimens from heavy smokers, at baseline and after 6 mo of treatment with 13-cis-retinoic acid (13-cis-RA) or placebo. Since we had previously detected **RAR**.beta. expression in 90% of bronchial specimens from nonsmokers, we considered loss of **RAR**.beta. mRNA expression in at least one of six biopsy specimens at baseline in this study to be aberrant. Results: **RAR**.beta. mRNA expression was aberrant in 30 (85.7%) of 35 subjects in the 13-cis-RA group and in 24 (72.7%) of 33 subjects in the placebo group. After 6 mo of 13-cis-RA treatment, the no. of subjects who were **RAR**.beta. pos. in all six biopsy specimens increased from five of 35 to 13 of 35 (2.6-fold), so that the percentage of individuals with aberrant **RAR**.beta. expression decreased to 62.9% (22 of 35), which represents a statistically significant difference from baseline expression (two-sided P = .01). In the placebo group, no statistically significant difference in **RAR** .beta. expression was obsd. between baseline and 6 mo. **RAR** .beta. expression was not related to current smoking status or reversal of squamous metaplasia. Conclusions: These results indicate that **RAR** .beta. is an independent marker of response to 13-cis-RA and may serve as an intermediate biomarker in chemoprevention trials of upper aerodigestive tract cancers.

ST **RAR** bronchial epithelium smoker retinoic acid; retinoic acid biomarker chemoprevention **lung** cancer

IT Retinoic acid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**RAR**-.beta.; nuclear **RAR**-.beta. in bronchial epithelium of smokers before and during chemoprevention)

IT Diagnosis
(cancer; nuclear **RAR**-.beta. in bronchial epithelium of smokers before and during chemoprevention)

IT Chemotherapy
(chemoprevention; nuclear **RAR**-.beta. in bronchial epithelium of smokers before and during chemoprevention)

IT Neoplasm
(diagnosis; nuclear **RAR**-.beta. in bronchial epithelium of smokers before and during chemoprevention)

IT Bronchi
(epithelium; nuclear **RAR**-.beta. in bronchial epithelium of smokers before and during chemoprevention)

IT Antitumor agents
Biomarkers (biological responses)
Tobacco smoke
(nuclear **RAR**-.beta. in bronchial epithelium of smokers before and during chemoprevention)

IT Cell proliferation
(squamous metaplasia; nuclear **RAR**-.beta. in bronchial epithelium of smokers before and during chemoprevention)

IT **Lung**
(type I cell, metaplasia; nuclear **RAR**-.beta. in bronchial epithelium of smokers before and during chemoprevention)
IT 4759-48-2, 13-cis-Retinoic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nuclear **RAR**-.beta. in bronchial epithelium of smokers before and during chemoprevention)

L18 ANSWER 4 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 132:58791 CA
TITLE: Retinoid-mediated suppression of tumor invasion and matrix metalloproteinase synthesis
AUTHOR(S): Schoenermark, Matthias P.; Mitchell, Teresa I.; Rutter, Joni L.; Reczek, Peter R.; Brinckerhoff, Constance E.
CORPORATE SOURCE: Dartmouth Medical School, Hanover, NH, 03755, USA
SOURCE: Annals of the New York Academy of Sciences (**1999**), 878(Inhibition of Matrix Metalloproteinases), 466-486
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cancer mortality usually results from the tumor invading the local environment and metastasizing to vital organs, e.g. liver, **lung**, and brain. Degrdn. of the extracellular matrix is, therefore, the sine qua non of tumor cell invasion, this degrdn. is mediated mainly by MMPs, and thus, inhibition of MMP synthesis is a target for anticancer agents. Tumor cells must traverse both the basement membrane (type IV collagen) and the interstitial stroma (type I collagen). Therefore, we used SEM to examine the invasive behavior of several aggressive tumor cell lines, A2058 melanoma cells, and SCC and FaDu squamous cell carcinomas through these matrixes; and we monitored the ability of all-trans retinoic acid and several **RAR**-specific ligands to block invasion. We demonstrate that several retinoids, which are specific **RAR** .alpha., .beta., or .gamma. agonists/antagonists, selectively inhibited MMP synthesis in the three tumor cell lines. However, there was not a common pattern of MMP inhibition by a particular retinoid. For instance, a **RAR**.alpha. antagonist suppressed MMP-1 and MMP-2 synthesis in the melanoma cell line, but not in the FaDu or SCC-25 cells. On the other hand, synthesis of MMP-1 and MMP-9 by the FaDu cells was affected hardly at all, while a **RAR**.gamma. antagonist reduced the levels of MMP-2. Only all-trans retinoic acid reduced MMP-1 synthesis in these cells. We postulate that the differences may be related to a differential pattern of **RAR** expression in each of these cells, and that the RARs expressed by each cell line may not be targets of these **RAR** specific compds. All-trans retinoic acid is a pan ligand, binding to all three RARs and, therefore, may **modulate** gene expression more generally. We conclude that the power of these new ligands lies in their specificity, which can be directed towards **modulating** expression of certain RARs and, thus, of certain MMPs. By blocking MMP synthesis, retinoids may be effective in cancer therapy by decreasing tumor invasiveness.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
SO Annals of the New York Academy of Sciences (**1999**), 878(Inhibition of Matrix Metalloproteinases), 466-486
CODEN: ANYAA9; ISSN: 0077-8923

AB Cancer mortality usually results from the tumor invading the local environment and metastasizing to vital organs, e.g. liver, **lung**, and brain. Degrdn. of the extracellular matrix is, therefore, the sine qua non of tumor cell invasion, this degrdn. is mediated mainly by MMPs, and thus, inhibition of MMP synthesis is a target for anticancer agents. Tumor cells must traverse both the basement membrane (type IV collagen) and the interstitial stroma (type I collagen). Therefore, we used SEM to examine the invasive behavior of several aggressive tumor cell lines, A2058 melanoma cells, and SCC and FaDu squamous cell carcinomas through these matrixes; and we monitored the ability of all-trans retinoic acid and several **RAR**-specific ligands to block invasion. We demonstrate that several retinoids, which are specific **RAR** .alpha., .beta., or .gamma. agonists/antagonists, selectively inhibited MMP synthesis in the three tumor cell lines. However, there was not a common pattern of MMP inhibition by a particular retinoid. For instance, a **RAR**.alpha. antagonist suppressed MMP-1 and MMP-2 synthesis in the melanoma cell line, but not in the FaDu or SCC-25 cells. On the other hand, synthesis of MMP-1 and MMP-9 by the FaDu cells was affected hardly at all, while a **RAR**.gamma. antagonist reduced the levels of MMP-2. Only all-trans retinoic acid reduced MMP-1 synthesis in these cells. We postulate that the differences may be related to a differential pattern of **RAR** expression in each of these cells, and that the RARs expressed by each cell line may not be targets of these **RAR** specific compds. All-trans retinoic acid is a pan ligand, binding to all three RARs and, therefore, may **modulate** gene expression more generally. We conclude that the power of these new ligands lies in their specificity, which can be directed towards **modulating** expression of certain RARs and, thus, of certain MMPs. By blocking MMP synthesis, retinoids may be effective in cancer therapy by decreasing tumor invasiveness.

ST antitumor antimetastatic retinoid MMP synthesis inhibitor; **RAR** extracellular matrix retinoate melanoma inhibitor; head neck carcinoma MMP retinoid receptor

IT Retinoic acid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**RAR**-.alpha.; retinoid-mediated suppression of tumor invasion and MMP synthesis)

IT Retinoic acid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**RAR**-.beta.; retinoid-mediated suppression of tumor invasion and MMP synthesis)

IT Retinoic acid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**RAR**-.gamma.; retinoid-mediated suppression of tumor invasion and MMP synthesis)

L18 ANSWER 5 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 131:295601 CA
TITLE: Means for the **modulation** of processes mediated by retinoid receptors, compounds useful therefor, preparation of compounds, and therapeutic use
INVENTOR(S): Evans, Ronald M.; Mangelsdorf, David J.; Heyman, Richard A.; Boehm, Marcus F.; Eichele, Gregor; Thaller, Christina
PATENT ASSIGNEE(S): The Salk Institute for Biological Studies, USA; Baylor College of Medicine; Ligand Pharmaceuticals, Inc.

SOURCE: U.S., 25 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5968989	A	19991019	US 1995-472817	19950607 <--

PRIORITY APPLN. INFO.: US 1995-472817 19950607
OTHER SOURCE(S): MARPAT 131:295601

AB Methods are provided to **modulate** processes mediated by retinoid receptors, employing high affinity, high specificity ligands for such receptors. The invention provides ligands which are more selective for the retinoid X receptor than is retinoic acid (i.e., rexoids). In another aspect of the invention, alternative ligands (other than retinoic acid) have been discovered which are capable of inducing retinoic acid receptor mediated processes. In yet another aspect, methods have been developed for the prepn. of such retinoid receptor ligands from readily available compds. The compds. are useful therapeutically for e.g. treatment of nonmalignant and malignant skin disorders.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Means for the **modulation** of processes mediated by retinoid receptors, compounds useful therefor, preparation of compounds, and therapeutic use

PI US 5968989 A **19991019**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5968989	A	19991019	US 1995-472817	19950607 <--

AB Methods are provided to **modulate** processes mediated by retinoid receptors, employing high affinity, high specificity ligands for such receptors. The invention provides ligands which are more selective for the retinoid X receptor than is retinoic acid (i.e., rexoids). In another aspect of the invention, alternative ligands (other than retinoic acid) have been discovered which are capable of inducing retinoic acid receptor mediated processes. In yet another aspect, methods have been developed for the prepn. of such retinoid receptor ligands from readily available compds. The compds. are useful therapeutically for e.g. treatment of nonmalignant and malignant skin disorders.

IT Apolipoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A-I; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CRABP (cellular retinoic acid-binding protein); **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Animal cell line
(F9; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Retinoic acid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**RAR**-.alpha.; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and

therapeutic use)
IT Retinoic acid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**RAR**-.beta.; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT Retinoic acid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**RAR**-.gamma.; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT Retinoid X receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RXR.alpha.; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT Retinoid X receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RXR.beta.; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT Retinoid X receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RXR.gamma.; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT Drosophila melanogaster
(Schneider cell line (S2); **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT Transcriptional regulation
(activation; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT Antitumor agents
(acute promyelocytic leukemia; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT Aging, animal
(and wrinkles; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT Antitumor agents
(carcinoma; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT Cell proliferation
(disorder; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT **Lung**, neoplasm
Lung, neoplasm
Skin, neoplasm
Skin, neoplasm
Testis, neoplasm
Testis, neoplasm
(inhibitors; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT Skin, disease
(keratinization; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT Skin

(keratinocyte; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Antitumor agents
Antitumor agents
(**lung**; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Antitumor agents
(melanoma; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Lipids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab.; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Acne
Antitumor agents
Cell differentiation
Drug delivery systems
Skin
Skin, disease
(**modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Retinoic acid receptors
Retinoid X receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Antitumor agents
(promyelocytic leukemia; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Antitumor agents
Antitumor agents
(skin; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Drug interactions
(synergistic; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Antitumor agents
Antitumor agents
(testis; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT 302-79-4, all-trans-Retinoic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT 5300-03-8P, 9-cis-Retinoic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PUR (Purification or recovery); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(**modulation** of processes mediated by retinoid receptors,

compds. useful therefor, compd. prepn., and therapeutic use)
IT 150737-17-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(**modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT 150643-13-3P 150737-18-1P, 4-keto-9-cis-Retinoic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT 150907-24-7P 151004-87-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT 39760-56-0 150907-23-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
IT 149958-05-4
RL: PRP (Properties)
(unclaimed nucleotide sequence; means for the **modulation** of processes mediated by retinoid receptors, compds. useful therefor, prepn. of compds., and therapeutic use)
IT 247116-03-6, PN: US5968989 SEQID: 1 unclaimed protein
RL: PRP (Properties)
(unclaimed protein sequence; means for the **modulation** of processes mediated by retinoid receptors, compds. useful therefor, prepn. of compds., and therapeutic use)

L18 ANSWER 6 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 131:168353 CA
TITLE: Identification of loci involved in accelerated wound healing and the development of new wound healing promoters
INVENTOR(S): Heber-Katz, Ellen
PATENT ASSIGNEE(S): The Wistar Institute, USA
SOURCE: PCT Int. Appl., 136 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9941364	A2	19990819	WO 1999-US2962	19990212	<--
WO 9941364	A3	19991223			

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,

FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2319700	AA	19990819	CA 1999-2319700	19990212 <--
AU 9926720	A1	19990830	AU 1999-26720	19990212 <--
EP 1053309	A1	20001122	EP 1999-906924	19990212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002503460	T2	20020205	JP 2000-531545	19990212
US 2003037345	A1	20030220	US 1999-249155	19990212

PRIORITY APPLN. INFO.:
US 1998-74737P A2 19980213
US 1998-97937P A2 19980826
US 1998-102051P A2 19980928
WO 1999-US2962 W 19990212

AB Genes that quant. improve the efficiency and effectiveness of wound healing in mice are identified. Wound healing is assayed by measuring the time taken for a 2 mm hole punched into the ear to heal. The genes or gene products may be useful in the development of new wound healing promoters, including agents for treatment of central and peripheral nerve wounds. Wound healing in the rapidly healing mouse line MRL was studied. In comparison to the C57BL/6 line, the MRL mice showed more extensive vascularization around wounds with rapid development of sebaceous glands and hair follicles and the unexpected appearance of adipocytes. These mice also showed improved healing of damage to the optic and sciatic nerve after crushing, and of the spinal cord after complete transection. Using the difference in wound healing behavior of the two lines, genetic polymorphisms assocd. with QTLs affecting wound healing were identified. The accelerated healing of the MRL line was lost with aging, and this appeared to be as a result of T-cell actions. Macrophages from the MRL accelerated wound healing in control mice.

PI WO 9941364 A2 **19990819**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9941364	A2	19990819	WO 1999-US2962	19990212 <--
WO 9941364	A3	19991223		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2319700	AA	19990819	CA 1999-2319700	19990212 <--
AU 9926720	A1	19990830	AU 1999-26720	19990212 <--
EP 1053309	A1	20001122	EP 1999-906924	19990212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002503460	T2	20020205	JP 2000-531545	19990212
US 2003037345	A1	20030220	US 1999-249155	19990212

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(LKLF (**lung** Kruppel-like zinc finger transcription factor), gene for, expression in healing wounds of; identification of loci involved in accelerated wound healing and development of new wound healing promoters)

IT Retinoic acid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**RAR**-.gamma., gene for, expression in healing wounds of; identification of loci involved in accelerated wound healing and

development of new wound healing promoters)
IT Apoptosis
Cell adhesion
Cell migration
Cell proliferation
Transcription, genetic
Translation, genetic
(**modulation** of, in acceleration of wound healing; identification of loci involved in accelerated wound healing and development of new wound healing promoters)
IT DNA formation
(replication, **modulation** of, in acceleration of wound healing; identification of loci involved in accelerated wound healing and development of new wound healing promoters)

L18 ANSWER 7 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 131:69157 CA
TITLE: Inhibition of hSP-B promoter in respiratory epithelial cells by a dominant negative retinoic acid receptor
AUTHOR(S): Ghaffari, Manely; Whitsett, Jeffrey A.; Yan, Cong
CORPORATE SOURCE: Division of Pulmonary Biology, Children's Hospital Medical Center, Cincinnati, OH, 45229-3039, USA
SOURCE: American Journal of Physiology (**1999**), 276(3, Pt. 1), L398-L404
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Retinoic acid (RA) receptors (RARs) belong to the nuclear hormone receptor superfamily and play important roles in **lung** differentiation, growth, and gene regulation. Surfactant protein (SP) B is a small hydrophobic protein synthesized and secreted by respiratory epithelial cells in the **lung**. Expression of the SP-B gene is **modulated** at the transcriptional and posttranscriptional levels. In the present work, immunohistochem. staining revealed that **RAR** -.alpha. is present on day 14.5 of gestation in the fetal mouse **lung**. To assess whether **RAR** is required for SP-B gene transcription, a dominant neg. mutant human (h) **RAR**-.alpha.403 was generated. The hRAR-.alpha.403 mutant was transcribed and translated into the truncated protein product by reticulocyte lysate in vitro. The mutant retained DNA binding activity in the presence of retinoid X receptor-.gamma. to an RA response element in the hSP-B promoter. When transiently transfected into pulmonary adenocarcinoma epithelial cells (H441 cells), the mutant hRAR-.alpha.403 was readily detected in the cell nucleus. Cotransfection of the mutant hRAR-.alpha.403 repressed activity of the hSP-B promoter and inhibited RA-induced surfactant proprotein B prodn. in H441 cells, supporting the concept that **RAR** is required for hSP-B gene transcription in vitro.
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
SO American Journal of Physiology (**1999**), 276(3, Pt. 1), L398-L404
CODEN: AJPHAP; ISSN: 0002-9513
AB Retinoic acid (RA) receptors (RARs) belong to the nuclear hormone receptor superfamily and play important roles in **lung** differentiation, growth, and gene regulation. Surfactant protein (SP) B is a small hydrophobic protein synthesized and secreted by respiratory epithelial cells in the **lung**. Expression of the SP-B gene is **modulated** at the transcriptional and posttranscriptional levels. In the present work, immunohistochem. staining revealed that **RAR** -.alpha. is present on day 14.5 of gestation in the fetal mouse

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ST SP B gene promoter transcription retinoate receptor **lung**

IT Retinoic acid receptors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**RAR**-.alpha.; retinoic acid receptor .alpha. in transcription activation of human surfactant protein B gene promoter in **lung**)

IT Gene, animal
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SP-B; retinoic acid receptor .alpha. in transcription activation of human surfactant protein B gene promoter in **lung**)

IT Surfactant proteins (pulmonary)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SP-B; retinoic acid receptor .alpha. in transcription activation of human surfactant protein B gene promoter in **lung**)

IT Transcriptional regulation
(activation; retinoic acid receptor .alpha. in transcription activation of human surfactant protein B gene promoter in **lung**)

IT **Lung**
(retinoic acid receptor .alpha. in transcription activation of human surfactant protein B gene promoter in **lung**)

IT Promoter (genetic element)
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(retinoic acid receptor .alpha. in transcription activation of human surfactant protein B gene promoter in **lung**)

L18 ANSWER 8 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 130:50438 CA
TITLE: Retinoid receptors and cancer
AUTHOR(S): Fontana, Joseph A.; Rishi, Arun K.
CORPORATE SOURCE: Department of Medicine and Cancer Center, University of Maryland at Baltimore, Baltimore, MD, USA
SOURCE: Advances in Organ Biology (**1997**), 3(Retinoids: Their Physiological Function and Therapeutic Potential), 219-230
CODEN: AOBIFW
PUBLISHER: JAI Press Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 66 refs. Retinoids display therapeutic efficacy in a no. of premalignant and malignant diseases. Retinoids **modulate** cellular phenotypes by binding to a no. of retinoic acid nuclear receptors (**RAR**.alpha., .beta., or .gamma.) or retinoic X nuclear receptors (RXR.alpha., .beta. or .gamma.). Most cells express more than one

RAR and RXR receptor. Various **RAR** and RXR subtypes activate different and distinct genes by binding to specific retinoid response elements located in the regulatory regions of target genes. **Modulation** of the expression of these receptors has a profound effect on the physiol. of the cells and their acquisition of a malignant phenotype. **RAR**.alpha. appears to regulate hematopoietic differentiation and its loss of mutation results in aberrant growth. **RAR**.beta. is expressed in both normal **lung** and breast tissue while **RAR**.beta. expression is lost in their malignant counterparts. The mechanism(s) involved in the loss of **RAR** .beta. in these tissues is unclear. Finally, **RAR**.alpha. expression in breast carcinoma is regulated by the estrogen receptor and its presence is necessary for the retinoic acid-mediated inhibition of growth.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Advances in Organ Biology (**1997**), 3(Retinoids: Their Physiological Function and Therapeutic Potential), 219-230
CODEN: AOBIFW

AB A review, with 66 refs. Retinoids display therapeutic efficacy in a no. of premalignant and malignant diseases. Retinoids **modulate** cellular phenotypes by binding to a no. of retinoic acid nuclear receptors (**RAR**.alpha., .beta., or .gamma.) or retinoic X nuclear receptors (RXR.alpha., .beta. or .gamma.). Most cells express more than one **RAR** and RXR receptor. Various **RAR** and RXR subtypes activate different and distinct genes by binding to specific retinoid response elements located in the regulatory regions of target genes. **Modulation** of the expression of these receptors has a profound effect on the physiol. of the cells and their acquisition of a malignant phenotype. **RAR**.alpha. appears to regulate hematopoietic differentiation and its loss of mutation results in aberrant growth. **RAR**.beta. is expressed in both normal **lung** and breast tissue while **RAR**.beta. expression is lost in their malignant counterparts. The mechanism(s) involved in the loss of **RAR** .beta. in these tissues is unclear. Finally, **RAR**.alpha. expression in breast carcinoma is regulated by the estrogen receptor and its presence is necessary for the retinoic acid-mediated inhibition of growth.

L18 ANSWER 9 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 129:258278 CA
TITLE: Retinoic acid-receptor activation of SP-B gene transcription in respiratory epithelial cells
AUTHOR(S): Yan, Cong; Ghaffari, Manely; Whitsett, Jeffrey A.; Zeng, Xin; Sever, Zvjezdana; Lin, Sui
CORPORATE SOURCE: Division of Pulmonary Biology, Children's Hospital Medical Center, Cincinnati, OH, 45229-3039, USA
SOURCE: American Journal of Physiology (**1998**), 275(2, Pt. 1), L239-L246
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Retinoids are known to play important roles in organ development of the **lung**. Retinoids exert their activity by **modulating** the expression of numerous genes, generally influencing gene transcription, in target cells. In the present work, the mechanism by which retinoic acid (RA) regulates surfactant protein (SP) B expression was assessed in vitro. RA (9-cis-RA) enhanced SP-B mRNA in pulmonary adenocarcinoma cells (H441 cells) and increased transcriptional activity of the SP-B promoter in both

H441 and mouse **lung** epithelial cells (MLE-15). Cotransfection of H441 cells with retinoid nuclear receptor (**RAR**)-.alpha., -.beta., and -.gamma. and retinoid X receptor (RXR)-.gamma. further increased the response of the SP-B promoter to RA. Treatment of H441 cells with RA increased immunostaining for the SP-B proprotein and increased the no. of cells in which the SP-B proprotein was detected. An RA responsive element mediating RA stimulating of the human SP-B promoter was identified. **RAR**-.alpha. and -.gamma. and RXR-.alpha. but not **RAR**-.beta. or RXR-.beta. and -.gamma. were detected by immunohistochem. anal. of H441 cells. RA, by activating **RAR** activity, stimulated the transcription and synthesis of SP-B in pulmonary adenocarcinoma cells.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO American Journal of Physiology (**1998**), 275(2, Pt. 1), L239-L246
CODEN: AJPHAP; ISSN: 0002-9513

AB Retinoids are known to play important roles in organ development of the **lung**. Retinoids exert their activity by **modulating** the expression of numerous genes, generally influencing gene transcription, in target cells. In the present work, the mechanism by which retinoic acid (RA) regulates surfactant protein (SP) B expression was assessed in vitro. RA (9-cis-RA) enhanced SP-B mRNA in pulmonary adenocarcinoma cells (H441 cells) and increased transcriptional activity of the SP-B promoter in both H441 and mouse **lung** epithelial cells (MLE-15). Cotransfection of H441 cells with retinoid nuclear receptor (**RAR**)-.alpha., -.beta., and -.gamma. and retinoid X receptor (RXR)-.gamma. further increased the response of the SP-B promoter to RA. Treatment of H441 cells with RA increased immunostaining for the SP-B proprotein and increased the no. of cells in which the SP-B proprotein was detected. An RA responsive element mediating RA stimulating of the human SP-B promoter was identified. **RAR**-.alpha. and -.gamma. and RXR-.alpha. but not **RAR**-.beta. or RXR-.beta. and -.gamma. were detected by immunohistochem. anal. of H441 cells. RA, by activating **RAR** activity, stimulated the transcription and synthesis of SP-B in pulmonary adenocarcinoma cells.

ST SPB transcription activation retinoate receptor **lung**; **lung** adenocarcinoma SPA SPC transcription activation

IT **Lung**, neoplasm
(adenocarcinoma; retinoic acid-receptor activation of SP-B gene transcription in respiratory epithelial cells)

L18 ANSWER 10 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 129:225149 CA
TITLE: Retinoic acid inhibits growth and enhances differentiation of testicular carcinoma cells
AUTHOR(S): Ueno, Munehisa; Deguchi, Nobuhiro
CORPORATE SOURCE: Department of Urology, Kidney Disease Center, Saitama Medical School, Japan
SOURCE: Molecular Urology (**1998**), 2(2), 49-55
CODEN: MOURFE; ISSN: 1091-5362
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB This review with 32 refs. summarizes our recent studies on the roles played by retinoic acid compds. in cell growth and differentiation of testicular cancers. In these cells, differentiation involves the prodn. of alpha-fetoprotein (AFP), which is known as extraembryonic differentiation. Very recently, we have established a testicular carcinoma cell line, KU-MT, from a **lung** metastasis. The KU-MT cells expressed the retinoic acid receptors (**RAR**)-.alpha. and

RAR-.gamma., and RXR-.alpha.. These RARs were upregulated in response to treatment with all-trans-retinoic acid (ATRA). Alpha-fetoprotein is continuously produced by these cells, whether they are grown in culture or as xenografts in nude mice. Treatments with ATRA caused elevation of AFP prodn. and inhibited the growth of KU-MT cells in vitro. The compd. also arrested the cell cycle in G1 and reduced the percentage of S-phase cells assocd. with wild-type p53, leading to a modest induction of apoptosis. The wild-type p53 protein may mediate the cell cycle and induce apoptosis when the cells differentiated. All-trans-retinoic acid and **RAR**-.alpha.-specific agonists upregulated the expression of laminin, a marker of endoderm differentiation, and the expression of 45 kDa bone morphogenetic protein-2, whereas arotinoid, which is not bound to **RAR**-.alpha., did not show any effects. In summary, retinoic acid compds. could **modulate** cell growth and differentiation of testicular cancers through their assocn. with **RAR**-.alpha..

SO Molecular Urology (**1998**), 2(2), 49-55
CODEN: MOURFE; ISSN: 1091-5362

AB This review with 32 refs. summarizes our recent studies on the roles played by retinoic acid compds. in cell growth and differentiation of testicular cancers. In these cells, differentiation involves the prodn. of alpha-fetoprotein (AFP), which is known as extraembryonic differentiation. Very recently, we have established a testicular carcinoma cell line, KU-MT, from a **lung** metastasis. The KU-MT cells expressed the retinoic acid receptors (**RAR**)-.alpha. and **RAR**-.gamma., and RXR-.alpha.. These RARs were upregulated in response to treatment with all-trans-retinoic acid (ATRA). Alpha-fetoprotein is continuously produced by these cells, whether they are grown in culture or as xenografts in nude mice. Treatments with ATRA caused elevation of AFP prodn. and inhibited the growth of KU-MT cells in vitro. The compd. also arrested the cell cycle in G1 and reduced the percentage of S-phase cells assocd. with wild-type p53, leading to a modest induction of apoptosis. The wild-type p53 protein may mediate the cell cycle and induce apoptosis when the cells differentiated. All-trans-retinoic acid and **RAR**-.alpha.-specific agonists upregulated the expression of laminin, a marker of endoderm differentiation, and the expression of 45 kDa bone morphogenetic protein-2, whereas arotinoid, which is not bound to **RAR**-.alpha., did not show any effects. In summary, retinoic acid compds. could **modulate** cell growth and differentiation of testicular cancers through their assocn. with **RAR**-.alpha..

L18 ANSWER 11 OF 16 CA

ACCESSION NUMBER: 127:16087 CA

TITLE: Suppression of retinoic acid receptor .beta. in non-small-cell **lung** cancer in vivo: implications for **lung** cancer development

AUTHOR(S): Xu, Xiao-Chun; Sozzi, Gabriella; Lee, Jin S.; Lee, J. Jack; Pastorino, Ugo; Pilotti, Silvana; Kurie, Jonathan M.; Hong, Waun K.; Lotan, Reuben

CORPORATE SOURCE: Departments of Tumor Biology and Clinical Cancer Prevention, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA

SOURCE: Journal of the National Cancer Institute (**1997**), 89(9), 624-629
CODEN: JNCIEQ; ISSN: 0027-8874

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Retinoids, analogs of vitamin A, are required for the normal growth and

differentiation of human bronchial epithelium. They are also able to reverse premalignant lesions and prevent second primary tumors in some patients with non-small-cell **lung** cancer (NSCLC). These effects are thought to result from **modulation** of cell growth, differentiation, or apoptosis (programmed cell death). When certain retinoid receptors in the cell nucleus, i.e., retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which mediate most retinoid actions are suppressed, abnormal activity may result that could enhance cancer development. This study was designed to det. whether there are abnormalities in the expression of retinoid receptors in surgical specimens from patients with NSCLC. Transcripts of nuclear retinoid receptors were detected in formalin-fixed, paraffin-embedded specimens by use of digoxigenin-labeled riboprobes specific for **RAR**.alpha., **RAR**.beta., **RAR**.gamma., RXR.alpha., RXR.beta., and RXR.gamma. for in situ hybridization to histol. specimens from 79 patients with NSCLC and as control from 17 patients with non-**lung** cancer. The quality and specificity of the digoxigenin-labeled probes were detd. by northern blotting, and the specificity of the binding of antisense riboprobes was verified by use of sense probes as controls. All receptors were expressed in at least 89% of control normal bronchial tissue specimens from 17 patients without a primary **lung** cancer and in distant normal bronchus specimens from patients with NSCLC. **RAR**.alpha., RXR.alpha., and RXR.gamma. were expressed in more than 95% of the NSCLC specimens. In contrast, **RAR**.beta., **RAR**.gamma., and RXR.beta. expression was detected in only 42%, 72%, and 76% of NSCLC, resp. Thus, the expression of **RAR**.alpha., RXR.alpha., and RXR.gamma. is not altered in NSCLC; however, expression of **RAR**.beta. and possibly also of **RAR**.gamma. and RXR.beta. is suppressed in a large percentage of patients with **lung** cancer. The loss of expression of one or more of these nuclear retinoid receptors may be assocd. with **lung** carcinogenesis.

TI Suppression of retinoic acid receptor .beta. in non-small-cell **lung** cancer in vivo: implications for **lung** cancer development

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NSCLC specimens. In contrast, **RAR**.beta., **RAR**.gamma., and RXR.beta. expression was detected in only 42%, 72%, and 76% of NSCLC, resp. Thus, the expression of **RAR**.alpha., RXR.alpha., and RXR.gamma. is not altered in NSCLC; however, expression of **RAR** .beta. and possibly also of **RAR**.gamma. and RXR.beta. is suppressed in a large percentage of patients with **lung** cancer. The loss of expression of one or more of these nuclear retinoid receptors may be assocd. with **lung** carcinogenesis.

ST **lung** cancer retinoate receptor

IT Retinoic acid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**RAR**-.alpha., mRNA; suppression of retinoic acid receptor .beta. in human non-small-cell **lung** cancer in vivo)

IT Retinoic acid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**RAR**-.beta., mRNA; suppression of retinoic acid receptor .beta. in human non-small-cell **lung** cancer in vivo)

IT Retinoic acid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**RAR**-.gamma., mRNA; suppression of retinoic acid receptor .beta. in human non-small-cell **lung** cancer in vivo)

IT Retinoid X receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RXR.alpha., mRNA; suppression of retinoic acid receptor .beta. in human non-small-cell **lung** cancer in vivo)

IT Retinoid X receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RXR.beta., mRNA; suppression of retinoic acid receptor .beta. in human non-small-cell **lung** cancer in vivo)

IT Retinoid X receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RXR.gamma., mRNA; suppression of retinoic acid receptor .beta. in human non-small-cell **lung** cancer in vivo)

IT **Lung**, neoplasm
(adenocarcinoma; suppression of retinoic acid receptor .beta. in human non-small-cell **lung** cancer in vivo)

IT Retinoid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mRNA; suppression of retinoic acid receptor .beta. in human non-small-cell **lung** cancer in vivo)

IT **Lung**, neoplasm
(non-small-cell carcinoma; suppression of retinoic acid receptor .beta. in human non-small-cell **lung** cancer in vivo)

IT mRNA
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(retinoid receptor; suppression of retinoic acid receptor .beta. in human non-small-cell **lung** cancer in vivo)

IT **Lung**, neoplasm
(squamous cell carcinoma; suppression of retinoic acid receptor .beta. in human non-small-cell **lung** cancer in vivo)

IT Cell nucleus
(suppression of retinoic acid receptor .beta. in human non-small-cell **lung** cancer in vivo)

L18 ANSWER 12 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 126:328891 CA
TITLE: **Modulation** of retinoic acid sensitivity in **lung** cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and their

heterodimerization

AUTHOR(S): Wu, Qiao; Li, Yin; Liu, Ru; Agadir, Anissa; Lee, Mi-Ock; Liu, Yi; Zhang, Xiao-kun

CORPORATE SOURCE: La Jolla Cancer Res. Cent., Burnham Inst., La Jolla, CA, 92037, USA

SOURCE: EMBO Journal (**1997**), 16(7), 1656-1669
CODEN: EMJODG; ISSN: 0261-4189

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The diverse function of retinoic acid (RA) is mediated by its nuclear receptors, the retinoic acid receptors (RARs) and retinoid X receptors (RXRs). However, the RA response is often lost in cancer cells that express the receptors. Previously, it was demonstrated that the RA response is regulated by the COUP-TF orphan receptors. Here, the authors present evidence that nur77, another orphan receptor whose expression is highly induced by phorbol esters and growth factors, is involved in **modulation** of the RA response. Expression of nur77 enhances ligand-independent transactivation of RA response elements (RAREs) and desensitizes their RA responsiveness. Conversely, expression of COUP-TF sensitizes RA responsiveness of RAREs by repressing their basal transactivation activity. Unlike the effect of COUP-TFs, the function of nur77 does not require direct binding of nur77 to the RAREs, but is through interaction between nur77 and COUP-TFs. The interaction occurs in soln. and results in inhibition of COUP-TF RARE binding and transcriptional activity. Unlike other nuclear receptors, a large portion of the carboxy-terminal end of nur77 is not required for its interaction with COUP-TF. In human **lung** cancer cell lines, COUP-TF is highly expressed in RA-sensitive cell lines while nur77 expression is assocd. with RA resistance. Stable expression of COUP-TF in nur77-pos., RA-resistant **lung** cancer cells enhances the inducibility of **RAR**.beta. gene expression and growth inhibition by RA. These observations demonstrate that a dynamic equil. between orphan receptors nur77 and COUP-TF, through their heterodimerization that regulates COUP-TF RARE binding, is crit. for RA responsiveness of human **lung** cancer cells.

TI **Modulation** of retinoic acid sensitivity in **lung** cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and their heterodimerization

SO EMBO Journal (**1997**), 16(7), 1656-1669
CODEN: EMJODG; ISSN: 0261-4189

AB The diverse function of retinoic acid (RA) is mediated by its nuclear receptors, the retinoic acid receptors (RARs) and retinoid X receptors (RXRs). However, the RA response is often lost in cancer cells that express the receptors. Previously, it was demonstrated that the RA response is regulated by the COUP-TF orphan receptors. Here, the authors present evidence that nur77, another orphan receptor whose expression is highly induced by phorbol esters and growth factors, is involved in **modulation** of the RA response. Expression of nur77 enhances ligand-independent transactivation of RA response elements (RAREs) and desensitizes their RA responsiveness. Conversely, expression of COUP-TF sensitizes RA responsiveness of RAREs by repressing their basal transactivation activity. Unlike the effect of COUP-TFs, the function of nur77 does not require direct binding of nur77 to the RAREs, but is through interaction between nur77 and COUP-TFs. The interaction occurs in soln. and results in inhibition of COUP-TF RARE binding and transcriptional activity. Unlike other nuclear receptors, a large portion of the carboxy-terminal end of nur77 is not required for its interaction with COUP-TF. In human **lung** cancer cell lines, COUP-TF is highly expressed in RA-sensitive cell lines while nur77 expression is

assocd. with RA resistance. Stable expression of COUP-TF in nur77-pos., RA-resistant **lung** cancer cells enhances the inducibility of **RAR**.beta. gene expression and growth inhibition by RA. These observations demonstrate that a dynamic equil. between orphan receptors nur77 and COUP-TF, through their heterodimerization that regulates COUP-TF RARE binding, is crit. for RA responsiveness of human **lung** cancer cells.

ST nur77 COUPTF retinoate sensitivity **lung** cancer; heterodimerization nur77 COUPTF retinoate sensitivity cancer

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(COUP-TF; **modulation** of retinoic acid sensitivity in **lung** cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)

IT Retinoic acid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**RAR**-.beta.; **modulation** of retinoic acid sensitivity in **lung** cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)

IT Genetic element
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RARE (retinoic acid-responsive element); **modulation** of retinoic acid sensitivity in **lung** cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)

IT Steroid receptors
Steroid receptors
Thyroid hormone receptors
Thyroid hormone receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TR (thyroid/steroid hormone receptor); **modulation** of retinoic acid sensitivity in **lung** cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)

IT Transcriptional regulation
(activation; **modulation** of retinoic acid sensitivity in **lung** cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)

IT Gene
(expression; **modulation** of retinoic acid sensitivity in **lung** cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)

IT Molecular association
(heterodimerization; **modulation** of retinoic acid sensitivity in **lung** cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)

IT **Lung**, neoplasm
(**modulation** of retinoic acid sensitivity in **lung** cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)

IT 302-79-4, Retinoic acid

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**modulation** of retinoic acid sensitivity in **lung** cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)

L18 ANSWER 13 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 126:207828 CA
TITLE: Retinoic acid receptor .epsilon. of human and expression of a cDNA encoding it and their therapeutic uses
INVENTOR(S): Cao, Liang; Ni, Jian; Fleischmann, Robert D.
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA
SOURCE: S. African, 49 pp.
CODEN: SFXXAB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
ZA 9404937	A	19950108	ZA 1994-4937	19940707 <--

PRIORITY APPLN. INFO.: ZA 1994-4937 19940707
AB A novel member of the human retinoic acid receptor family, **RAR** .epsilon., is identified and characterized and a cDNA encoding it is cloned and expressed. The receptor or the cDNA are of use in the diagnosis and treatment of diseases assocd. with abnormal levels of the receptor or of retinoic acid (no data) or in the identification of **modulators** of receptor activity. The mRNA for the receptor is abundant in testis, placenta, spleen, thymus and **lung**.
PI ZA 9404937 A **19950108**

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IT **Lung**
Placenta
Spleen
Testis
Thymus gland
(retinoic acid receptor .epsilon. mRNA in; retinoic acid receptor .epsilon. of human and expression of cDNA encoding it and their therapeutic uses)
IT Retinoic acid receptors
RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(.epsilon., (**RAR**.epsilon.); retinoic acid receptor .epsilon. of human and expression of cDNA encoding it and their therapeutic uses)

L18 ANSWER 14 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 123:246782 CA

TITLE: TGF-.beta. **modulates** the expression of retinoic acid-induced **RAR**-.beta. in primary cultures of embryonic palate cells
AUTHOR(S): Nugent, Paul; Potchinsky, Merle; Lafferty, Cynthia; Greene, Robert M.
CORPORATE SOURCE: Dep. Pathology, Anatomy Cell Biol., Jefferson Med. Coll., Philadelphia, PA, 19107, USA
SOURCE: Experimental Cell Research (**1995**), 220(2), 495-500
CODEN: ECREAL; ISSN: 0014-4827
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have previously shown that both transforming growth factor-.beta. (TGF-.beta.) and retinoic acid (RA) regulate the expression of cellular retinoic acid binding proteins (CRABP) I and II and TGF-.beta.3 mRNAs in primary cultures of murine embryonic palate mesenchymal (MEPM) cells. The authors now describe addnl. cross-talk between the RA and TGF-.beta. signal transduction pathways-the ability of TGF-.beta., including the endogenous form(s), to **modulate** the expression of the nuclear retinoic acid receptor-.beta. (**RAR** -.beta.). Northern blot hybridization revealed that RA induced the expression of **RAR**-.beta. mRNA, there being little or no detectable expression in untreated MEPM cells. Induction by 3.3 .mu.M RA was abrogated by simultaneous treatment with TGF-.beta.1 (5 ng/mL). TGF-.beta.1 alone had no effect on **RAR**-.beta. mRNA expression. Detn. of **RAR**-.beta. mRNA half-life by treatment with actinomycin D indicated that TGF-.beta.1 did not alter the stability of **RAR** -.beta. mRNA. Conditioned medium (CM) from MEPM cells contained little active TGF-.beta. protein; heat treatment of the CM dramatically increased the amt. of active TGF-.beta. as assessed by the mink **lung** epithelial cell bioassay. Furthermore, heat- or acid-activated CM also inhibited CRABP-I and RA-induced **RAR**-.beta. expression. The effect of heat-activated conditioned medium could be abrogated with panspecific neutralizing antibodies to TGF-.beta., confirming that endogenous TGF-.beta. is the biol. active factor in heat-activated CM. These results provide evidence for complex interactions between TGF-.beta. and RA in the regulation of gene expression of embryonic palatal cells and suggest a role for endogenous TGF-.beta. in the regulation of expression of genes encoding elements of the RA signal transduction pathway.

TI TGF-.beta. **modulates** the expression of retinoic acid-induced **RAR**-.beta. in primary cultures of embryonic palate cells
SO Experimental Cell Research (**1995**), 220(2), 495-500
CODEN: ECREAL; ISSN: 0014-4827
AB The authors have previously shown that both transforming growth factor-.beta. (TGF-.beta.) and retinoic acid (RA) regulate the expression of cellular retinoic acid binding proteins (CRABP) I and II and TGF-.beta.3 mRNAs in primary cultures of murine embryonic palate mesenchymal (MEPM) cells. The authors now describe addnl. cross-talk between the RA and TGF-.beta. signal transduction pathways-the ability of TGF-.beta., including the endogenous form(s), to **modulate** the expression of the nuclear retinoic acid receptor-.beta. (**RAR** -.beta.). Northern blot hybridization revealed that RA induced the expression of **RAR**-.beta. mRNA, there being little or no detectable expression in untreated MEPM cells. Induction by 3.3 .mu.M RA was abrogated by simultaneous treatment with TGF-.beta.1 (5 ng/mL). TGF-.beta.1 alone had no effect on **RAR**-.beta. mRNA expression. Detn. of **RAR**-.beta. mRNA half-life by treatment with actinomycin D indicated that TGF-.beta.1 did not alter the stability of **RAR** -.beta. mRNA. Conditioned medium (CM) from MEPM cells contained little

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IT Signal transduction, biological
Teratogens
(TGF-.beta. **modulates** expression of retinoic acid-induced **RAR**-.beta. in primary cultures of embryonic palate cells)

IT Ribonucleic acids, messenger
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(for retinoic acid receptor-.beta.; TGF-.beta. **modulates** expression of retinoic acid-induced **RAR**-.beta. in primary cultures of embryonic palate cells)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CRABP-I (cellular retinoic acid-binding protein I), TGF-.beta. **modulates** expression of retinoic acid-induced **RAR** -.beta. in primary cultures of embryonic palate cells)

IT Receptors
Retinoid receptors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**RAR**-.beta. (retinoic acid receptor .beta.), TGF-.beta. **modulates** expression of retinoic acid-induced **RAR** -.beta. in primary cultures of embryonic palate cells)

IT Animal growth regulators
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-transforming growth factors, TGF-.beta. **modulates** expression of retinoic acid-induced **RAR**-.beta. in primary cultures of embryonic palate cells)

IT 302-79-4, Retinoic acid
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(TGF-.beta. **modulates** expression of retinoic acid-induced **RAR**-.beta. in primary cultures of embryonic palate cells)

L18 ANSWER 15 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 122:154423 CA
TITLE: Ubiquitous receptor: a receptor that **modulates** gene activation by retinoic acid and thyroid hormone receptors
AUTHOR(S): Song, Ching; Kokontis, John M.; Hiipakka, Richard A.; Liao, Shutsung
CORPORATE SOURCE: The Ben May Inst. Dep. Biochem. Mol. Biol., Univ. Chicago, Chicago, IL, 60637, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1994**), 91(23), 10809-13
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The cDNA for a member of the nuclear receptor family was cloned and named ubiquitous receptor (UR), since UR protein and mRNA are detected in many cell types. Rat UR/human retinoid X receptor .alpha. (hRXR.alpha.) heterodimers bound preferentially to double-stranded oligonucleotide direct repeats having the consensus half-site sequence AGGTCA and 4-nt spacing (DR-4). Coexpression of UR in COS-1 cells inhibited the stimulation of chloramphenicol acetyltransferase (CAT) reporter gene expression by hRXR.alpha. and human retinoic acid receptor .alpha. in the presence of all-trans-retinoic acid when DR-4 (but not DR-5) was present upstream of the promoter of a CAT reporter gene (DR-4-CAT). UR expression also inhibited the activation of a DR-4-CAT reporter gene by hRXR.alpha. and 9-cis-retinoic acid or by thyroid hormone receptor .beta. in the presence of thyroid hormone. However, in the absence of 9-cis-retinoic acid, UR in combination with hRXR.alpha. stimulated DR-4-CAT expression. Coexpression of thyroid hormone receptor markedly reduced this stimulation in the absence of thyroid hormone. UR may play an important role in normal growth and differentiation by **modulating** gene activation in retinoic acid and thyroid hormone signaling pathways.

TI Ubiquitous receptor: a receptor that **modulates** gene activation by retinoic acid and thyroid hormone receptors

SO Proceedings of the National Academy of Sciences of the United States of America (**1994**), 91(23), 10809-13
CODEN: PNASA6; ISSN: 0027-8424

AB The cDNA for a member of the nuclear receptor family was cloned and named ubiquitous receptor (UR), since UR protein and mRNA are detected in many cell types. Rat UR/human retinoid X receptor .alpha. (hRXR.alpha.) heterodimers bound preferentially to double-stranded oligonucleotide direct repeats having the consensus half-site sequence AGGTCA and 4-nt spacing (DR-4). Coexpression of UR in COS-1 cells inhibited the stimulation of chloramphenicol acetyltransferase (CAT) reporter gene expression by hRXR.alpha. and human retinoic acid receptor .alpha. in the presence of all-trans-retinoic acid when DR-4 (but not DR-5) was present upstream of the promoter of a CAT reporter gene (DR-4-CAT). UR expression also inhibited the activation of a DR-4-CAT reporter gene by hRXR.alpha. and 9-cis-retinoic acid or by thyroid hormone receptor .beta. in the presence of thyroid hormone. However, in the absence of 9-cis-retinoic acid, UR in combination with hRXR.alpha. stimulated DR-4-CAT expression. Coexpression of thyroid hormone receptor markedly reduced this stimulation in the absence of thyroid hormone. UR may play an important role in normal growth and differentiation by **modulating** gene activation in retinoic acid and thyroid hormone signaling pathways.

IT Adrenal gland
Brain
Heart
Kidney
Liver
Lung
Ovary
Prostate gland
Spleen
Testis
Uterus
Vagina
(mRNA expression; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)

IT Fibroblast
(skin; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)

IT Protein sequences

[redacted]

Rat
Signal transduction, biological
(ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Ribonucleic acids, messenger
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Thyroid hormones
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Ribonucleic acid formation factors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(ubiquitous receptor; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Animal cell line
(3T3, ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Animal cell line
(BJAB, human B-cell; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Animal cell line
(LNCaP, prostate carcinoma; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Animal cell line
(PC-3, prostate carcinoma; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Receptors
Retinoid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**RAR**-.alpha. (retinoic acid receptor .alpha.), ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Animal cell line
(RPMI-1788, ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Retinoid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RXR.alpha. (retinoic acid receptor X .alpha.), ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RXR.alpha. (retinoid X receptor .alpha.), ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Animal cell line
(WEHI-231, mouse immature B-cell; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and

thyroid hormone receptors)
IT Deoxyribonucleic acid sequences
(complementary, ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(thyroid hormone .beta., ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT Thyroid hormone receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta., ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT 159845-69-9 159845-70-2 159845-71-3 159845-72-4 159845-73-5 159845-74-6 159845-75-7
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA binding site; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT 159966-44-6, Ribonucleic acid factor (rat clone R6.2) 159966-45-7
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(amino acid sequence; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT 159199-63-0 161050-10-8
RL: PRP (Properties)
(nucleotide sequence; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
IT 302-79-4, all-trans-Retinoic acid 5300-03-8, 9-cis-Retinoic acid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)

L18 ANSWER 16 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 112:230122 CA
TITLE: Indirect effects of histamine on pulmonary rapidly adapting receptors in cats
AUTHOR(S): Yu, Jun; Roberts, Andrew M.
CORPORATE SOURCE: Sch. Med., Univ. Louisville, Louisville, KY, 40292, USA
SOURCE: Respiration Physiology (**1990**), 79(2), 101-10
CODEN: RSPYAK; ISSN: 0034-5687
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The relative importance of **lung** mech. changes during histamine-induced activation of pulmonary rapidly adapting receptors (RARs) was investigated. In anesthetized, open-chest, artificially ventilated cats, the authors recorded **RAR** activity and injected histamine (25-50 .mu.g/kg) into the right atrium. Histamine initially increased **RAR** activity from 1.1 to 3.6 imp/s at 15.6 s when dynamic **lung** compliance (CDYN) was decreased by 29.1%. The firing pattern of RARs changed from a relatively irregular pattern to a pronounced respiratory **modulation**. **RAR** activity reached its peak (5.6 imp/s) at 36.3 s. The firing pattern further

changed to a cardiac **modulation**, and the activity closely correlated with cardiac output. On comparing the initial response of RARs to histamine with the response to mech. decreasing CDYN, the activities were similar when CDYN was decreased by the same amt. In cats, the initial increase of **RAR** activity in response to histamine is apparently related to **lung** mech. changes, but the later increase is related to cardiovascular functions.

SO Respiration Physiology (**1990**), 79(2), 101-10
CODEN: RSPYAK; ISSN: 0034-5687

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ST histamine **lung** rapidly adapting receptor; cardiovascular system **lung** histamine; receptor **lung** compliance histamine

IT Blood pressure
(histamine effect on, **lung** rapidly adapting receptors in relation to)

IT **Lung**, composition
(rapidly adapting receptors of, histamine effect on)

IT 51-45-6, Histamine, biological studies
RL: BIOL (Biological study)
(**lung** rapidly adapting receptors response to)

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	59.23	87.60

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-11.78	-13.02

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